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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/158,272	09/22/98	DIAS	V 10806-64

HM12/0816

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/158,272	Dias Et. Al.
Examiner	**Group Art Unit**
Joseph Woitach	1632

☐ Responsive to communication(s) filed on _____.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *27-33 and 35-60* is/are pending in the application.

Of the above, claim(s) *29, 30, and 51* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *27, 28, 31-33, 35-50, and 52-60* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed May 27, 2000, paper number 10, has been received and entered. Claim 34 has been canceled. Claims 27, 28, 33, 37-40, 43, 48-50 and 52 have been amended. Claims 53-60 have been added. Claims 29, 30 and 51 have been withdrawn from consideration. Claims 27, 28, 33, 35-50 and 52-60 are currently under examination.

Oath/Declaration

A new corrected declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date has been filed.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The amendment to the specification has obviated the previous rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 31-50 are rejected, and claims 28, 52, 54 and 56-59 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of using beta recombinase in mammalian cells which contain the HMG1 protein, it does not reasonably provide enablement for all eukaryotic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants argue that the specification, page 9, lines 3-30, supports the use of beta recombinase in eukaryotic cells because it is capable of using factors provided by the cell in order to exhibit recombination between two six sites. Additionally, claims 53, 55 and 60 have been added to specifically recite that the factor needed is HMG1. See amendment page 6. Applicants arguments have be considered but not found persuasive.

As detailed in the specification and the previous office action, the necessity of HMG1 and/or Hbsu is absolute for the resolution of the recombination event catalyzed by beta recombinase. As taught by Alonso *et al.*, the Hbsu is required for the resolution and DNA inversion mediated by beta recombinase (JBC page 938; abstract), and that E.coli HU and/or mammalian HMG1 can substitute for Hbsu as a chromatin associated protein for *in vitro* mediated recombination (Molecular Microbiology page 471; abstract). Alonso *et al.* teach that this is a strict requirement, and that in the absence of HU (in HU-deficient E. coli) or of another chromatin associated protein such as HMG1, recombination does not occur (JBC page 2943; figure 5). Neither the prior art nor the applicants demonstrate that beta recombinase is capable of mediating

site-specific recombination in the absence of one of these proteins, therefore, any eukaryotic cell lacking expression of one of these proteins would be incapable of a recombination event (for example cells from the HMG1 knock-out mouse in Calogero *et al.*). It may be that other proteins will substitute for this requirement, however, this is not taught in the specification. It is clear that beta recombinase will catalyze a recombination event between two six sites when the appropriate factors such as HMG1 and Hbsu are present, however, it is not clear that these factors are present, or that the naturally occurring homologs are present, in any and all eukaryotic cells. In the absence of at least one of these factors in a eukaryotic cell which does not endogenously contain HMG1 or Hbsu, it is not clear if one could practice the method in the full scope of the claim.

Therefore, for the reasons presented above and in the previous office action, the rejection is maintained.

Claim 52 previously rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicants amendment to claim 52 from a method for developing transgenic animals to one which reads only on transgenic mammalian cells obviates the previous rejection. However, it

should be noted, as discussed above, that only cells which contain the appropriate factors, such as HMG1 and Hbsu, are capable of exhibiting a beta recombinase recombination event.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 28, 33, 35-42, 48, 50, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

The amended claims 27, 28 are unclear in the recitation of 'mediating intramolecular recombination' because while the specification supports the use of beta recombinase and the proper cofactors for resolution (i.e. HMG-1 and/or Hbsu) to mediate recombination between two six sites, it is unclear how addition of beta recombinase would mediate any and all recombination in the eukaryotic cells. Steps which specifically clearly define the recombination event to be mediated by the addition of beta recombinase and the appropriate cofactors are needed.

The amended claim 33 is vague unclear in its recitation of "two or more different specific recombination events at a time are promoted". The specification is clear in that the presence of beta recombinase and the appropriate factors result in a recombination event between two intramolecularly located *six* sites. It is unclear how "two or more different" events could occur in

this context. Further, it is unclear if the recombination is to occur between these two target sites or that the recombination occurs at each site independently of the other.

The amended claims 39-40 are unclear in its recitation of "target sequences". The specification teaches that recombination occurs between *six* sites and no other recognition sequences have been described or defined. Without functional language that defines the direct repeat sequences as recognition sites for beta recombinase it is unclear what is encompassed by 'target' sequences.

The amended claim 52 is unclear and incomplete. Them claim recites a method for the development of transgenic mammalian cells, however the amended step is unclear in how selecting a eukaryotic cell from a group of mammalian cells would result in a transgenic mammalian cell. Step(s) which describe selection of the mammalian cells carrying the transgene are needed.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 57 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 56. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

All claims are free from the art. Applicants were the first to isolate and describe the beta recombinase from the resolvase/invertase family and the first to describe the method of use of beta recombinase in mammalian cells demonstrating that the mammalian HMG1 can serve as the required chromatin associated protein for resolution of site-specific recombination events.

Claims 55 and 60 would be found allowable if rewritten as independent claims.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is 1(703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Joseph T. Woitach

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER